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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,239	10/18/2001	Rita De Santis	2818-64	6035

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/22/2002 8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/981,239	DE SANTIS, RITA	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication app ars on th cover sheet with th correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 32-48 are pending in the application.

This Office Action is in response to the amendment filed on 7/23/02.

Response to Amendment

The rejection of claims 1-18 under 35 U.S.C.112, first paragraph has been withdrawn in light of Applicants cancellation of the claims.

The rejection of claims 8, 15 and 16 under 35 U.S.C.112, second paragraph has been withdrawn in light of Applicants cancellation of the claims.

The objection to the abstract has been withdrawn in light of Applications' submission of a new abstract.

Claims 32-48 are rejected under 35 U.S.C.112, first paragraph for reasons discussed below.

Claims 32-47 are rejected under 35 U.S.C.112, second paragraph for reasons discussed below.

Claim 48 is objected to for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

Claims 32-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for generating antigen presenting cells (APC) expressing cancer testis antigen (CTA); wherein the APC is generated from tumor patients peripheral blood mononuclear cells (PMBC), does not reasonably provide enablement for a method of generating APC expressing CTA, wherein the APC is generated from cells from a healthy subject. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The nature of the invention is a method for generating APC cells expressing CTA by treating APC with hypomethylating agent. The specification discloses a method for generating APC cells expressing TAA belong to cancer-testis antigen (CTA) family by treating cells derived from PBMC of cancer patients with advanced stage of disease or healthy individual, with demethylating agent 5-aza-2-deoxcytidine (see examples 1-6).

The breath of the claims is very broad. The claims encompass a method for generating APC from any cell expressing CTA by treating activated APC with hypomethylating agents. However, the guidance in the specification is limited. The specification only discloses that the APC (from peripheral blood mononuclear cells) expressing a number of TAAs from CTA subfamily. The specification fails to disclose that whether the cells expressing tumor antigen are from healthy individual or cancer patients. The specification also fails to teach whether the claimed method can generate CTA expressing APC from sources other than PBMC, such as fibroblast, keratinocyte or any other adult stem cells.

The state of art at the time of filing teaches there are a number of TAAs associated with human cancer (see Moigeon, 2001,Vaccine, 19: 1305-1326, table 3), including CTAs, mutated antigens, overexpressed antigens. Some of them are expressed by a variety of tumors (such as CTAs), whereas others are tumor specific (e.g. Mum1 and Caspase 8). Although the mechanism for all TAA expression is not completely understood at present, several pathways have been proposed and it appears that different mechanisms might be involved. For example, the activation of some members of the CTA family such as MAGE antigens have been associated

with global hypomethylation in tumor cells (see page 1311, bridging paragraph of col.1 and 2). On the other hand, Moingeon also teach that TAAs can be expressed following activation of a cryptic promoter within intronic sequence (e.g. NA 17-A in melanoma), pseudogene processing (e.g. melanoma NA 88-A) or frameshift mutation resulting in the utilization of alternative open reading frames (e.g. colon carcinoma associated antigens). In addition, TAAs also include carbohydrates, gangliosides, glyco lipids and mucins. Moreover, there are seven subfamilies within CTA family, each includes multiple genes (see Kirkin et al. 2002, Cancer Investigation, 20 (2): 222-236). At present, the mechanism for tumor specific expression of these genes is not known (see page 230, col. 2, 2nd paragraph, lines 1-2) except for MAGE, GAGE and LAGE, which are activated in tumor cells treated with 5-aza-2-deoxycytidine. However, the same treatment of normal diploid cells does not up-regulate the expression of MAGE1 gene (see page 230, Col.2, 2nd paragraph, line 7-9). Kirkin et al. point out that existing data on the induction of MAGE expression in normal cells are contradictory and that further investigation is needed (see page 230-231, bridging paragraph). The specification does not teach that treating normal APC cells or any other normal cells such as CD34+ cells, fibroblasts or stem cells as claimed with 5-aza-2-deoxycytidine would induce CTA expression. The specification also fails to teach whether these CTA expressing cells are generated from patients with advanced disease or normal individual. Therefore, the induction of CTA expression in APC cells derived from normal individual by hypomethylating agent is unpredictable. In addition, the generation of APC cells expressing CTA from fibroblasts, keratinocytes, or any kind of stem cells is also unpredictable.

Due to the lack of guidance from the specification and prior art, one skilled in the art would have to engage in undue amount of experimentation to practice the claimed invention commensurate in scope with these claims.

In response to Applicants argument that the present invention provides a method for expressing CTAs in non-tumor cells, the Examiner disagrees that this assertion is supported by the instant specification. The data presented in the 12 tables that was allegedly extracted from the instant specification cannot be located in the instant specification. For example, the title of Example 1 in the instant specification is "ADHAPI-Cells/B-EBV, PMBC purification." However, the title of Example 1 presented in the instant Amendment is "ADHAPI-Cells/B-EBV, RT-PCR analysis of CTA expressed by ADHAPI-Cells/B-EBV and control B-EBV cells." In addition, none of the tables matches any tables in the instant specification. Applicants are invited to indicate specific locations of the specification in which the data in the 12 tables can be found. As such, arguments based on these data cannot be considered persuasive. Therefore, the 112 first paragraph rejection still applies to claims 32-48 (see reasons discussed above).

New Grounds of Rejection Necessitated by Applicants' Amendemnt

Claim Rejections - 35 USC § 112

Claims 32-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding clams 32-47, the term "cancer-testis antigen presenting cells" renders the claims indefinite because it is unclear what subject Applicants are referring to. In other word, it

is unclear if it is antigen presenting cells expressing cancer testis antigen or antigen presenting cells isolated from cancer testis. Clarification is required.

The term "multiple tumor associated antigens" also renders the claims indefinite. Claim 32 recites "a method of generating of cancer testis antigen presenting cells" in line one. It is unclear how the cells would concomitantly express "multiple tumor associated antigens" after hypomethylating agent treatment.

Regarding claim 38, the term "shared cancer testis antigens" renders the claims indefinite because it is unclear what are cancer testis antigens shared by. In addition, the recitation of "wherein said cells express shared cancer testis antigens" also renders the claims indefinite. The claim is drawn to a method of generating APC expressing cancer testis antigen by treating APC with hypomethylating agents. If the cells already expresses cancer testis antigen, why does the cells need further treatment?

Claim Objections

Claim 48 is objected to as being dependent upon a cancelled base claim (1). Applicant is advised to rewrite the claim in independent form including all of the limitations of (canceled) base claim (1).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
October 21, 2002

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600